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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 08/822,033 | 03/24/1997 | WAYNE A. MARASCO | 43471-FWC | 5884 |

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| EXAMINER | |
|---|---|
| WOITACH, JOSEPH T | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | 36 |

DATE MAILED: 05/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 08/822,033 | Applicant(s) MARASCO ET AL. | |
|---|---|---|---|
| | Examiner Joseph Woitach | Art Unit 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☒ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

File



*Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 26, 2002, paper number 34, has been entered.

**DETAILED ACTION**

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph T. Woitach** and the group art unit is now **1632**.

Applicants' amendment filed February 26, 2002, paper number 35 has been received and entered. Claims 1 and 3-16 are pending and currently under examination.

*Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5 and 7-16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Beug *et al.*, Chaudhary *et al.* and Wu *et al.*

Applicants note that the instant invention comprises a fusion protein containing both a targeting moiety which binds to a cell surface epitope and a binding moiety for a nucleic acid. Applicant argue that such a delivery system is not suggested by the prior art which focuses on chemical conjugates. Summarizing Beug *et al.* and Wu *et al.*, Applicants note that each teach a system which uses the chemical synthesis to conjugate a targeting moiety to polylysine, wherein the polylysine forms a non-covalent bond with the DNA. Applicants argue that the synthesis of protein targeting molecules and DNA binding compounds such as polylysine can be subject to variability and difficulty encountered in chemical synthesis. Applicants argue the bond that joins the targeting moiety and the nucleic acid binding moiety is inherently more stable than the non-covalent bonds taught in Beug *et al.* and Wu *et al.* Applicants provide a recent publication by the instant inventors and note that results comparing various formulations for delivery, and conclude that the results demonstrate that use of a fusion protein less efficient, it is more cell specific (pointing to Figures 6A and 7). With respect to modifying the particular working examples in both Beug *et al.* and Wu *et al.*, Applicants argue that the suggestion by Wu *et al.* to

form conjugates with antibodies is only passing, and that both Beug *et al.* and Wu *et al.* more particularly suggest the use of glycoprotein, and that the skilled artisan would not be taught to use an antibody. Finally Applicants argue that the methods of Chaudhary *et al.* are not directed to methods of delivering polynucleotides rather to the isolation and delivery of single chain antibody-immunotoxins conjugates. See Applicants amendment, pages 1-4. Applicants' arguments have been fully considered but not found persuasive.

First, it should be noted that polylysine and other protamines are proteins capable of binding nucleic acids. Second, contrary to Applicants summary of Beug *et al.* and Wu *et al.*, the bonds between the targeting moiety and nucleic acid moiety are exactly the same. Upon review of Beug *et al.* and Wu *et al.*, and as noted in Applicants amendment, the conjugates taught in each of the references are coupled by **covalent** bonds, not non-covalent bonds. The only reference to a non-covalent bonds is in description of the interaction of a protamine (nucleic acid binding moiety) and the nucleic acid, which the instant invention also encompasses. Further, Beug *et al.* do teach that the conjugates can be made either by chemical synthesis or recombinant methods (pages 7-9; bridging paragraphs through page 9). Wu *et al.* teach covalent linkages by the formation of disulfide bounds. Additionally, it is noted that the instantly claimed invention is not limited to how the fusion protein is made, and encompasses fusion proteins made by any means, chemical conjugation, chemical synthesis and/or expression products of recombinant vectors. Applicants arguments against the means of conjugation are not found persuasive,

because the instant claims also encompass these methods of synthesis and additionally, Beug *et al.* does specifically teach to use recombinant methods.

In review of Applicants post-filing work, Examiner finds the Applicants arguments and conclusion of the results incomplete. First, Figure 6A demonstrates that a truncated ScFv protamine conjugate (ScFv-P-S) is more effective in targeting than the full-length ScFv protamine conjugate (ScFv-P-L) or the ScFv alone (ScFv), which explained by the incorrect folding of the ScFv-P-L and the inability of ScFv alone to bind DNA (page 559; second column). With respect to Figure 7, the conjugates tested do not compare ScFv-P-L and non-covalent conjugates, rather it test various formulations of mixtures for the ability of the ScFv to embed properly into the complex. Examiner would concede that different formulations provide a different specificity of targeting, however one can not reasonably compare the results of Figures 6 and 7 and conclude that chemical conjugates are less specific than recombinantly generated conjugates. Additionally, it is noted that the instant claims encompass conjugates made both recombinantly and chemically. Applicants' arguments are not found persuasive because post filing results by the instant inventors do not provide any unexpected results over the teachings of the cited references, and in fact encompass any obvious shortcoming or strengths related to chemical conjugation because the instant claims encompass any method of generating the fusion protein.

In response to applicant's argument that one skilled in the art would not take the specific reference of Wu *et al.* to use an antibody for the targeting of polynucleotide complex to a

particular cell is not found persuasive. Clearly, both Beug *et al.* and Wu *et al.* are concerned with the ability of effectively targeting a polynucleotide to a desired cell. As specifically taught in Wu *et al.*, and recognized in the art at the time of filing, an antibody in any form provides a effective means for specifically identifying and binding an epitope. Further, it should be noted that one of skill in the art at the time of filing would know that antibodies are glycosylated and thus, glycoproteins (though neither Beug *et al.* and Wu *et al.* teach this). Further, the skilled artisan would view the teachings of each reference as a whole as carrier systems for the targeting of nucleic acids into mammalian cells, and not simply limited to particular working examples provided.

Applicants arguments that Chaudhary *et al.* is nonanalogous art is not persuasive. The courts have held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the teachings of Chaudhary *et al.* have been relied upon to demonstrate fusion proteins comprising an antibody moiety were known and made at the time of filing. Examiner notes that while Wu *et al.* suggest the use of antibodies in the conjugate, neither Beug *et al.* nor Wu *et al.* provide the specific teaching for the generation of such a fusion protein. Chaudhary *et al.* has been relied upon only for the support and demonstration that the suggestion by Wu *et al.* could effectively be practiced at the time of the claimed invention.

In summary, Beug *et al.* disclose a nucleic acid carrier, which is a fusion protein consisting of transferrin fused to a polycationic polypeptide, used in complexes with a nucleic acid molecule. Wu *et al.* teach a nucleic acid carrier consisting of a cell-receptor specific ligand linked to a polycationic polypeptide, and demonstrate successful use of this carrier to deliver and express DNA to a specific cell type *in vivo*. Further, Wu *et al.* suggest that an antibody could be used as targeting moiety, that protamine could be used as the polycationic polypeptide, and that a peptide bond could be used to link the targeting and DNA binding moieties. Chaudhary *et al.* disclose a fusion protein which consists of a single chain antibody having a truncated form of PEA (containing domain III) fused to its carboxyl end. This fusion protein is used to deliver PEA specifically to cells expressing the surface antigen recognized by the antibody. Chaudhary *et al.* teach a method for cloning antibody genes, a method for producing and purifying the fusion protein, and that a fusion protein containing an antibody against the interleukin-2 receptor was used for the selectively delivery to cells expressing the receptor.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the prior art to develop the claimed compositions and methods. Both Beug *et al.* and Wu *et al.* disclose a nucleic acid carrier, which is a fusion protein consisting of targeting protein conjugated to a polycationic polypeptide, used in complexes with a nucleic acid molecule. Further, Wu *et al.* specifically suggest the use of other targeting molecules, including antibodies for the targeting of the complexes. Additionally, Chaudhary *et al.* demonstrate that at the time of filing, the art recognized that antibodies could be

used to specifically target a cell of interest, and thus, could have accomplished the suggest of Wu *et al.* for the use of other targeting proteins.

Thus, for the reasons above and of record, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 6 stands rejected under 35 U.S.C. § 103 as being unpatentable over Beug *et al.*, Chaudhary *et al.* and Wu *et al.* as applied to claims 1, 3-5 and 7-16 above, and further in view of Ryder *et al.*

Applicants argue that Ryder et al. do not overcome the essential deficiencies of Beug *et al.*, Chaudhary *et al.* and Wu *et al.* as discussed above. See Applicants' amendment, page 4. Applicants' arguments have been fully considered but not found persuasive.

As discussed above in detail the combined teachings of Beug *et al.*, Chaudhary *et al.* and Wu *et al.* make obvious the invention set forth in claims 1,3-5 and 7-16. Both Beug *et al.* and Wu *et al.* teach that other DNA binding proteins can be used ( Beug *et al.* pages 6-7 and Wu *et al.* column 4), however neither teach the specific proteins recited in claim 6. Ryder *et al.* has been relied upon to demonstrate that the general teaching for the use of a DNA binding protein set forth in Beug *et al.* and Wu *et al.* can be specifically accomplished by using the DNA-binding regions of three *jun* proteins (Fig. 2) and the nucleotide sequence of *jun-D* cDNA (Fig. 1). Ryder *et al.* teach that a fusion protein comprising the *jun* DNA-binding moiety is capable of effectively binding DNA and thus, would be effective in the fusion protein complexes of Beug *et*

*al.* Chaudhary *et al.* and Wu *et al.* Ryder *et al.* is not relied upon to correct the deficiencies of Beug *et al.* Chaudhary *et al.* and Wu *et al.*, rather, Ryder *et al.* is used to demonstrate that other DNA binding domains were known at the time of filing and in the context of a fusion protein were effective in binding DNA. The teachings of Beug *et al.* and Wu *et al.* are not limiting to the various nucleic acid binding moieties and targeting moieties contemplated, and one of skill in the art would be motivated to use the appropriate moieties depending on the nucleic acid and/or cell to be targeted. Ryder *et al.* provides the specific evidence that at the time of filing a fusion protein comprising the DNA binding domain of *jun* is effective in binding DNA. Given the general teach of both Beug *et al.* and Wu *et al.* to use other proteins for the binding of DNA, Applicants' arguments are not persuasive because they do not suggest why one would not use the teachings of Ryder *et al.*, nor does the instant disclosure does not provide any evidence that the use of *jun* in a particular conjugate provides any unexpected result not demonstrated in Ryder *et al.*

Thus, for the reasons above and of record, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

***Conclusion***

No claim is allowed.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been

finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630